

## Toxicity of Starch Administered by Mouth

ELDON M. BOYD, M.D. and SHEAN-JANG LIU, B.Sc.,  
Kingston, Ont.

**I**N view of a recent report in *Time* entitled "An Urge for Argo",<sup>1</sup> studies in our laboratory on the toxicity of starch given orally to albino rats are of interest. Argo refers to Argo Gloss Starch, a form of cornstarch, which is eaten in large amounts by Negro women and especially pregnant women living in the United States of America; these women are described as "starch addicts".

The habit of eating huge quantities of starch appears to have evolved from clay-eating, a form of pica. In the folklore of the 16th to 19th centuries, eating clay was believed to be of value against several diseases; to produce beautiful children when eaten by pregnant women, and to give mental relief from the cares and worries of life. Among the Negroes of the southern U.S.A., laundry starch replaced clay and the habit passed from one generation to the next. Satisfaction from eating starch is said to be akin to that derived from chewing gum or smoking tobacco, and the amount eaten may vary from less than one pound per week to over four pounds per day. The remaining diet may be deficient in essential nutrients, and anemia is common. Further information may be found in recent reviews.<sup>2-6</sup>

Starch addiction is confined almost exclusively to adults, and must be distinguished from the much more serious condition which results from feeding weanlings a diet high in starch and correspondingly low in protein which produces stunted growth and death. The latter condition was believed by Czerny and Keller<sup>7</sup> in 1909 to be caused by excess starch intake, but it is now ascribed to deficient protein intake and is commonly called kwashiorkor. This protein deficiency syndrome can be reproduced in animals.<sup>8</sup> On the other hand, we have found in preliminary studies that doses of starch up to one-third of body weight rarely produce death in young adult albino rats.<sup>9</sup>

### METHODS

The experiments were performed upon CBL male albino rats weighing  $140 \pm 15$  (mean  $\pm$  S.D.) g., which were fed Purina laboratory

chow checkers and water *ad libitum*. The animals were segregated, one to a metabolism cage, before the administration of starch. Starch was used in the form of Starch, Soluble, Fisher Certified A.C.S., prepared by digesting potato starch in boiling water, filtering and evaporating the filtrate to yield soluble starch of low amylose content.<sup>10</sup> This is a fine white powder which contains 18% water, less than 0.3% ash and a negligible amount of pulp and fibre. It was given to the animals in the form of a starch paste containing 60 g. of starch mixed with distilled water to a final volume of 100 ml. and kept at body temperature and in suspension on a Fisher Thermix Stirring Hot Plate until ready for use. Concentrations greater than 60% (w/v) gradually solidified and could not be forced through the intragastric cannula.

No deaths resulted from the intragastric administration of the 60% starch paste in volumes from 50 to 100 ml. per kg. body weight, but larger doses produced gastric rupture. Volumes of from 50 to 100 ml. per kg. were then given in pilot tests at intervals of from one to five hours. It was found that a dose of 50 ml. per kg. every 2½ hours for four administrations (a total of 120 g. per kg. of starch) did not produce gastric rupture, while a dose of 70 ml. per kg. every 2½ hours for four administrations (a total of 168 g. per kg. of starch) produced gastric rupture in half of the animals during the first day of administration. It was also found that animals which did not have gastric rupture after the first day on the larger dose of starch could be given increasing volumes per kg. of 60% starch paste on subsequent days.

Based upon these preliminary trials, starch was given daily for 14 consecutive days in total daily oral doses of 36, 72, 120 and 168 g. per kg. and in animals which did not succumb to gastric rupture in doses gradually increasing to 204, 240 and 288 g. per kg. Each dose was divided into four equal parts and each part was given at intervals of 2½ hours. Each dose was given to 12 to 40 rats so that there were at least 10 survivors per dosage group at 14 days. Volume controls were given the same volume per kg. of distilled water, i.e., from 60 to 480 ml. per kg. per day for 14 days, 10 animals per volume group. A second set of 10 controls received gastric tube insertions only, four times a day at 2½-hour intervals for 14 days, and the third group of 10 controls received no treatment

From the Department of Pharmacology, Queen's University, Kingston, Ontario.

This project was supported by grants MT 1183 and MA 2713 of the Medical Research Council of Canada.

Reprint requests to: Dr. Eldon M. Boyd, Head, Department of Pharmacology, Queen's University, Kingston, Ontario.

TABLE I.—WET WEIGHT† AND WATER CONTENT‡ OF THE GASTROINTESTINAL ORGANS OF ALBINO RATS FOLLOWING INTRAGASTRIC ADMINISTRATION OF 60% STARCH PASTE OR DISTILLED WATER (DW) DAILY FOR 14 DAYS§

Organ and measurement	Group	Daily dose of starch (1st subheading line, g. per kg.) or distilled water (2nd subheading line, ml. per kg.)			
		36	72 - 120	168 - 204	240 - 288
		60	120 - 200	280 - 340	400 - 480
Cardiac stomach, weight	Starch	- 2.6	+ 5.6**	+49.6**	+ 87.7**
Cardiac stomach, weight	D.W.	+ 4.0	+22.5††	+95.1††	+135.1††
Cardiac stomach, water	Starch	- 5.0	+ 1.6	+ 5.2	+ 13.0
Cardiac stomach, water	D.W.	+ 2.4	+ 0.4	+ 7.2††	+ 13.1††
Pyloric stomach, weight	Starch	-26.9*	-19.1**	-18.7**	- 8.0**
Pyloric stomach, weight	D.W.	-16.8††	- 7.2†	+ 4.7	+ 12.2††
Pyloric stomach, water	Starch	- 3.3	+ 0.1*	+ 4.2	+ 6.0
Pyloric stomach, water	D.W.	+ 1.2	- 4.5†	- 0.2	+ 8.5††
Small bowel, weight	Starch	+ 5.5	+46.9**	+68.2**	+ 78.8**
Small bowel, weight	D.W.	+ 0.8	+12.9†	+19.2††	+ 21.4††
Small bowel, water	Starch	+ 6.2	+ 0.6*	+ 4.7**	+ 5.9*
Small bowel, water	D.W.	+ 2.5	- 4.1†	- 5.3†	+ 1.1
Cecum, weight	Starch	- 0.5	+40.1**	+51.5**	+ 72.3**
Cecum, weight	D.W.	- 7.9	+ 3.4	- 5.2	- 1.7
Cecum, water	Starch	+11.2*	+ 9.8*	+17.1**	+ 22.0**
Cecum, water	D.W.	+ 4.3	- 1.7	+ 1.6	+ 10.3††
Colon, weight	Starch	- 3.3*	+ 8.3**	+12.9**	+ 31.7**
Colon, weight	D.W.	-20.0††	- 2.0	-11.5†	- 7.0
Colon, water	Starch	+ 5.0	- 2.1**	+ 5.6**	+ 5.2**
Colon, water	D.W.	+ 4.0	- 7.0†	- 6.2†	- 4.4

†Wet weight was measured in g.

‡Water content was measured as g. water per 100 g. dry weight of tissue.

§The results are expressed as mean per cent change from controls given daily gastric tube insertions only, specifically as  $(\bar{X}_d - \bar{X}_c) / \bar{X}_c \times 100$  where  $\bar{X}_d$  is the mean in rats given starch or distilled water and  $\bar{X}_c$  is the mean in controls receiving only gastric tube insertions. In rats given starch, \* indicates that the mean per cent change was significantly different from that in rats given distilled water at  $P = 0.05$  to  $0.02$  and \*\* at  $P = 0.01$  or less. In rats given distilled water, † indicates that  $\bar{X}_d - \bar{X}_c$  was significant at  $P = 0.05$  to  $0.02$  and †† at  $P = 0.01$  or less.

except for measurements in metabolism cages. To determine an ultimate cause of death other than gastric rupture or regurgitation asphyxia, 41 rats were given gradually increasing daily dosages of starch until death occurred, after which autopsies were performed; blood hemoglobin was determined at intervals.

Clinical measurements were recorded daily for 14 days and included body weight in g., food consumption in g. chow per kg. body weight per 24 hours, water intake in ml. per kg. per 24 hours, colonic temperature in degrees Fahrenheit, urinary volume in ml. per kg. per 24 hours, urinary glucose and protein output in mg. per kg. per 24 hours, urinary pH on 24-hour samples, and other clinical signs as they appeared, and were graded as 1+ to 4+. Colonic temperature was recorded by a Thermistemp Telethermometer and urinalyses were performed using Ames Combistix Reagent strips.

Gross pathology was recorded on all animals that died. Weights and water levels of organs listed in Tables I and III were measured on survivors and controls at 14 days. The sample of skeletal muscle was the right half of the muscle layer of the ventral abdominal wall. The contents of the lumen of the gastrointestinal tract were removed before weighing. Water levels

were measured on aliquots dried to constant weight at 95° C. in a Fisher Forced-Draft Iso-temp oven and were calculated as g. per 100 g. dry weight of tissue. The sample of skin for water analysis was taken from the dorsolumbar region. After removal of the organs listed in Tables I and III, the residual carcass was cut into small pieces and homogenized in a Waring blender, and a sample was used for water analysis. Histopathological examinations were made upon blocks of tissue fixed in Lillie's buffered formalin, and sections were stained with hematoxylin-phloxine-saffron. Statistical methods were those of Croxton.<sup>11</sup>

## RESULTS

Data on clinical measurements are summarized in Table II. Values in rats given starch or distilled water have been compared with corresponding values in rats given gastric tube insertions. Insertion of the intragastric cannula four times a day for 14 days produced a slight but significant inhibition of growth and a decrease in water intake, urinary volume and urinary pH when compared with rats that were given no treatment. The animals became accustomed to gastric tube insertion and gradually offered little or no resistance, so that the measured effects of

TABLE II.—DAILY CLINICAL MEASUREMENTS AND OBSERVATIONS IN ALBINO RATS GIVEN STARCH AS A 60% PASTE BY STOMACH TUBE AND IN CONTROLS GIVEN DISTILLED WATER DAILY FOR 14 DAYS†

		36 N = 10+ 10 controls	72 - 120 N = 20+ 10 controls	168 - 204 N = 20+ 10 controls	240 - 288 N = 20+ 10 controls
Starch: g. per kg. per day	Group				
		60 N = 10+ 10 controls	120 - 200 N = 20+ 10 controls	280 - 340 N = 20+ 10 controls	400 - 840 N = 20+ 10 controls
Water: ml. per kg. per day					
Body weight.....	Starch	+ 0.5	— 8.2*	— 14.6**	— 14.9**
Body weight.....	Water	— 3.9††	— 4.9††	— 7.6††	— 10.2††
Food (chow) intake.....	Starch	— 14.3**	— 21.4**	— 31.0**	— 27.5**
Food (chow) intake.....	Water	— 3.8†	— 6.0††	— 4.8†	— 5.4†
Water intake.....	Starch	+ 8.2**	— 12.6*	— 2.8**	— 9.3**
Water intake.....	Water	— 4.2	— 17.6††	— 17.3††	— 17.3††
Body temperature.....	Starch	— 0.4	— 1.0	— 0.8	— 0.7
Body temperature.....	Water	— 1.1	— 1.0	— 0.8	— 0.9
Urinary volume.....	Starch	+ 23**	+ 11**	+ 103**	+ 142**
Urinary volume.....	Water	+ 111††	+ 362††	+ 712††	+ 963††
Urinary pH.....	Starch	+ 14.8*	+ 15.1**	+ 15.3**	+ 6.3
Urinary pH.....	Water	+ 22.2††	+ 10.2††	+ 10.8††	+ 4.0†
Urinary blood.....	Starch	absent	absent	absent	absent
Urinary blood.....	Water	absent	absent	present	present
Irritability on days 1 and 2.....	Starch	absent	absent	present	present
Drowsiness on days 1 and 2.....	Starch	absent	absent	present	present
Pallor on days 1 and 2.....	Starch	absent	absent	present	present
Hyporeflexia on days 1 and 2.....	Starch	absent	absent	present	present
Epistaxis on days 1 and 2.....	Starch	absent	absent	present	present
Abdominal bloating on days 1 and 2.....	Starch	absent	absent	present	present
Gastric rupture (days 1 and 2).....	Starch	absent	absent	present	present
Death from pneumonia.....	Starch	absent	absent	present	absent
Death from gastrointestinal obstruction...	Starch	absent	absent	present	present

† Numerical results are expressed as mean per cent change from controls given gastric tube insertion only, specifically as  $(\bar{X}_d - \bar{X}_c) / \bar{X}_c \times 100$  where  $\bar{X}_d$  is the mean of 14 days of readings in rats given starch paste or distilled water and  $\bar{X}_c$  the corresponding mean in rats given gastric tube insertions only. In animals given starch, \* indicates that the mean per cent change was significantly different from that in rats given water at  $P = 0.05$  to  $0.02$  and \*\* at  $P = 0.01$  or less. In rats given distilled water, † indicates that  $\bar{X}_d - \bar{X}_c$  differed from zero at  $P = 0.05$  to  $0.02$  and †† at  $P = 0.01$  or less. Clinical signs entered as present or absent were absent in all rats given distilled water except as noted.

tube insertion were probably due to mild psychic trauma or to interference with sleep patterns.

Increasing daily doses of starch produced increasing inhibition of growth and decreasing intake of laboratory chow, both changes being in part due to the effects of the large volume of water given with the starch. Water produced a marked diuresis, alkaluria and decrease in water intake which occurred to the same or lesser degrees in animals fed starch paste. Both water and starch produced a slight decrease in body temperature which was significant when results for all doses were averaged but not for any one dose. Water also produced a hematuria at the higher doses.

In addition to inhibition of growth, starch variously caused irritability, drowsiness, pallor, hyporeflexia, epistaxis and abdominal bloating on the first two days of administration. These signs appeared to be associated with gastric distension, since most deaths from gastric rupture occurred at this time. Gastric rupture appeared in 50 to 75% of rats given starch in amounts of 168 g. per kg. and over. Of the survivors of gastric rupture, 5% died of pneumonia and 20% from bowel obstruction during the 14 days of starch administration.

Autopsy at 14 days revealed that rats adapted themselves to administration of large daily volumes of starch paste by enlargement of the gastrointestinal tissues, as shown in Table I. Enlargement of cardiac stomach also occurred in rats given the distilled water vehicle (that is, it was a response to liquid volume introduced into the stomach); the increase was mainly in dry weight, but large doses produced some hydration of gastric tissues. The pyloric or glandular part of the stomach was decreased in weight by starch administration owing to a decrease in dry weight of tissue.

When starch paste entered the small bowel, water was absorbed and the starch was pelleted into calculi and covered with mucus. The large pellets or calculi distended the bowel, and the extra work involved in propelling them along the intestine produced a marked hypertrophy of the muscularis mucosae and muscularis externa, as illustrated in Figs. 1a and 2a and c. As a result, there followed a marked increase in the weight of the small bowel, cecum and colon of starch-treated rats as indicated in Table I. Very large volumes of distilled water were not quickly absorbed from the small bowel, and the resulting distension produced some hypertrophy of in-



Fig. 1a



Fig. 1b

Fig. 1.—Photomicrographs illustrating (a) starch-induced hypertrophy of the muscularis mucosae and muscularis externa of cardiac stomach compared with that seen in (b) a normal rat of the same body weight.

testinal smooth muscle but not to the same extent as that produced by the starch pellets. Distilled water had left the bowel before it

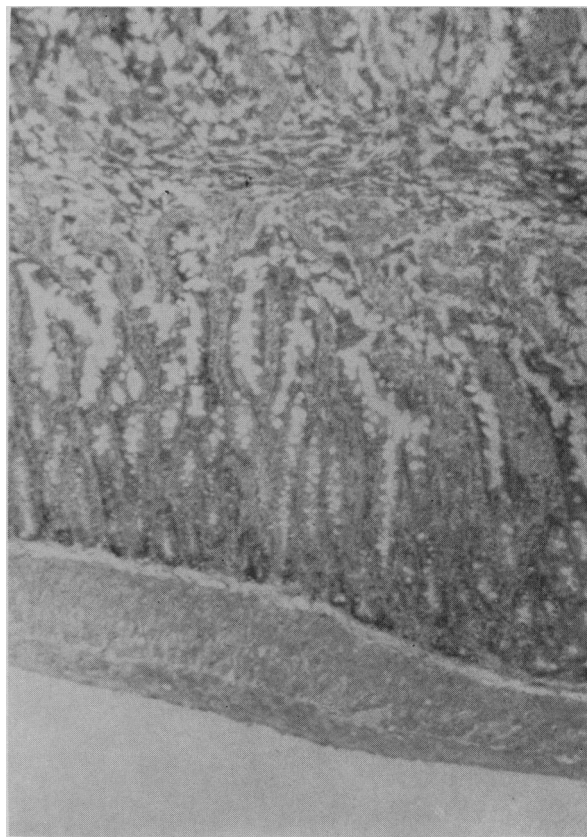


Fig. 2a

reached the cecum and colon, which were not hypertrophied and actually lost weight at some doses as shown in Table I. Compared with distilled water controls, the greatest hypertrophy occurred in the cecum, then in the small bowel and least in the colon, as illustrated in Fig. 3. The water levels of the small bowel, cecum and colon tended to become somewhat increased in rats given starch but rarely in rats given only distilled water, in which they were sometimes decreased (Table I).

Shifts in weight of the remaining body organs are summarized in Table III. Large amounts of starch or distilled water produced a stress reaction as manifested by an increase in weight of the adrenal glands and a decrease in that of the thymus gland and spleen. The lungs, salivary glands and testicles and especially the brain were relatively resistant to loss of weight, the skin was particularly susceptible, and other organs lost weight at about the same rate as the residual carcass. Hypertrophy of the salivary glands, reported by Merkatz<sup>3</sup> in a woman who ate excessive amounts of starch, was not seen in these animals given starch directly into the stomach.

Data on water contents of remaining body organs are summarized in Table IV. While large

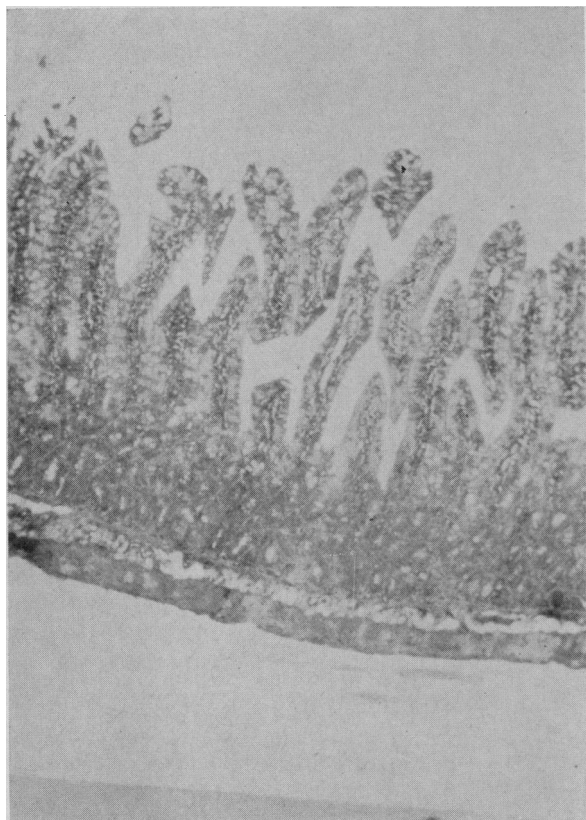


Fig. 2b

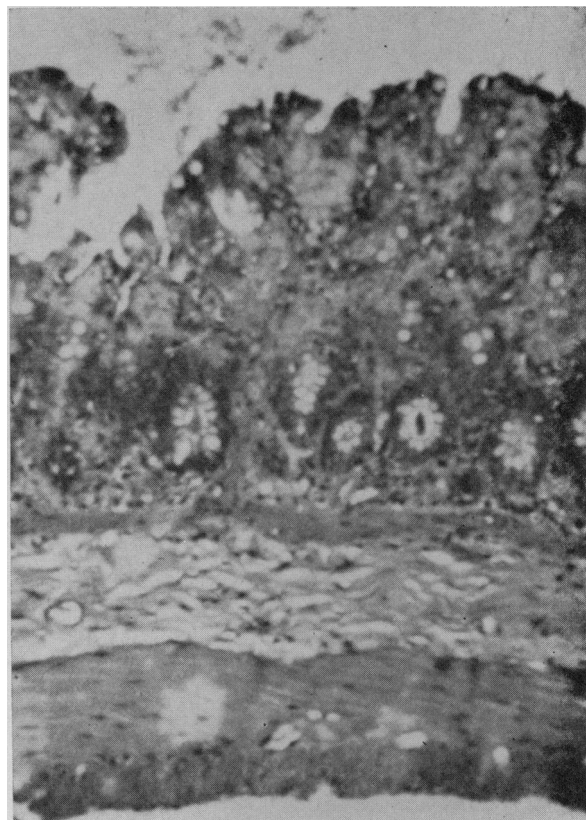


Fig. 2d

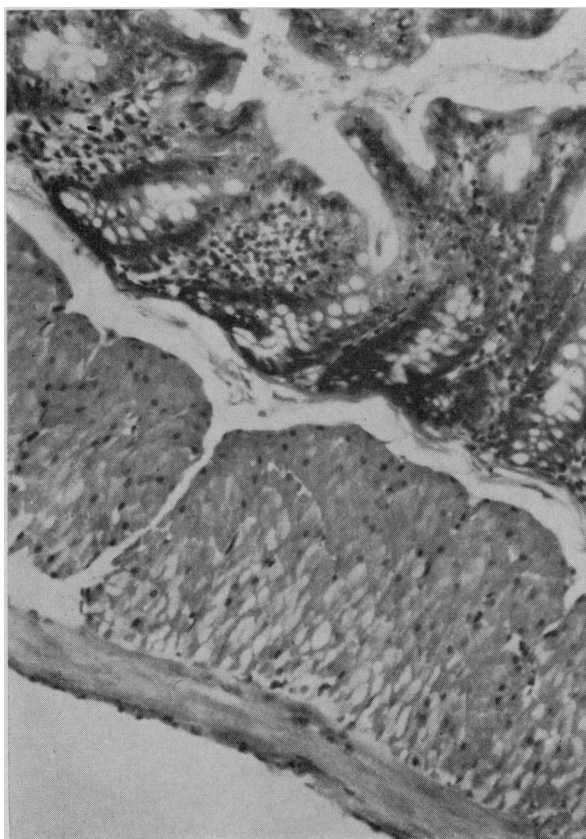


Fig. 2c

Fig. 2.—Photomicrographs illustrating (a) starch-induced hypertrophy of smooth muscle of the small bowel and (c) cecum compared with that seen in a normal rat of the same body weight (b and d).

doses of starch produced some hydration of gastrointestinal tissues, the most common effect on other body organs was a slight dehydration due mainly to the effect of water in the administered starch paste.

In animals given progressively larger daily doses of starch for periods longer than 14 days, the causes of death were impaction of starch in the stomach or intestine or both, or pneumonia, if one excludes animals which died from stomach rupture or from regurgitation of starch paste with aspiration into the lungs and death from asphyxia. Deaths due to gastrointestinal impaction and obstruction from daily doses of starch of from 168 to 456 g. per kg. occurred between the 2nd and 49th days. Net body weight declined during the day before death; the weight of retained starch was subtracted from total body weight to obtain net body weight. Blood hemoglobin had not declined in any of these animals.

Histologically, the hypertrophy of smooth muscle in the gastrointestinal tract was found mostly in the inner circular muscle layer of the muscularis externa of the small bowel, cecum and colon (Figs. 2a and c). The stratified squamous epithelium and muscularis mucosae of

TABLE III.—WEIGHT OF BODY ORGANS IN ALBINO RATS AFTER 14 DAYS OF DAILY ORAL ADMINISTRATION OF STARCH AND OF DISTILLED WATER (DW)†

Organ	Group	Daily dose of starch (1st subheading line, g. per kg.) or distilled water (2nd subheading line, ml. per kg.)			
		36	72 - 120	168 - 204	240 - 288
		60	120 - 200	280 - 340	400 - 480
Adrenal glands.....	Starch	+2.9	+ 7.8	+ 7.0	+15.2
Adrenal glands.....	D.W.	+3.1	+ 6.0	- 1.5	+19.2††
Brain.....	Starch	-0.5	- 1.9	- 5.5*	- 5.4
Brain.....	D.W.	+1.0	- 0.9	- 2.6	- 3.4†
Heart.....	Starch	+6.1	-11.3**	-21.0**	-22.2**
Heart.....	D.W.	—	- 3.4	- 5.5†	- 7.3††
Kidneys.....	Starch	+2.9*	-14.5*	-26.0**	-22.9**
Kidneys.....	D.W.	-5.8	- 7.9†	-13.3††	-15.1††
Liver.....	Starch	+3.3*	-12.4**	-21.2**	-21.1**
Liver.....	D.W.	-5.9	+ 1.9	- 6.2†	-12.4††
Lungs.....	Starch	-6.0*	- 8.7*	- 6.7	-14.9**
Lungs.....	D.W.	+5.8	- 1.8	- 3.4	- 3.8
Muscle (ventral abdominal wall).....	Starch	-9.5	-15.2	-22.6*	-27.1**
Muscle (ventral abdominal wall).....	D.W.	—	-12.3††	-14.2††	-17.4††
Skin.....	Starch	+0.8	-18.0**	-30.0**	-34.1**
Skin.....	D.W.	-2.2	- 2.7	-11.5††	-18.3††
Spleen.....	Starch	+4.4	-10.1	-35.3**	-36.2**
Spleen.....	D.W.	-1.7	- 6.4	-13.3††	-20.6††
Submaxillary salivary glands.....	Starch	+6.0	+ 0.1	-12.0**	-18.5**
Submaxillary salivary glands.....	D.W.	—	+ 5.4	+ 2.5	- 1.5
Testicles.....	Starch	+1.9	- 3.3	- 8.2*	-11.8*
Testicles.....	D.W.	+0.2	- 2.2	- 3.8	- 7.5††
Thymus gland.....	Starch	-6.5	-17.5**	-41.9**	-46.3**
Thymus gland.....	D.W.	+0.8	+ 1.2	-16.9††	-16.9††
Residual carcass.....	Starch	-0.4	-11.0*	-20.8**	-24.8**
Residual carcass.....	D.W.	-3.3	- 4.5†	- 7.8††	-14.3††

†Weight of organs was fresh weight measured in g. The results are expressed as mean per cent change from controls given only gastric tube insertions, specifically as  $(\bar{X}_d - \bar{X}_c) / \bar{X}_c \times 100$  where  $\bar{X}_d$  is the mean in rats given starch or distilled water and  $\bar{X}_c$  the mean in tube-insertion controls. In animals given starch, \* indicates that the mean per cent change was significantly different from that in rats given distilled water at  $P = 0.05$  to  $0.02$  and \*\* at  $P = 0.01$  or less. In rats given distilled water, † indicates that  $\bar{X}_d - \bar{X}_c$  was significant at  $P = 0.05$  to  $0.02$  and †† at  $P = 0.01$  or less.

cardiac stomach were also hypertrophied (Fig. 1a). The lamina propria and submucosa were hyperemic. A mild, diffuse fatty degeneration or early necrosis was occasionally present in the liver, and small areas of venous stasis and capillary hemorrhage were occasionally noted in the kidneys. Mild degrees of hyperemia or capillary-venous congestion were found in some adrenal glands, testicles, thymus glands, hearts, lungs and salivary glands. These minor changes were seen in controls given distilled water. In general, therefore, the microscopic appearance of body organs was normal or almost normal apart from gastrointestinal hypertrophy.

#### DISCUSSION AND CONCLUSIONS

The oral toxicity of starch was studied in this laboratory as part of a program designed to measure the toxicity of common foodstuffs in albino rats. This program in turn followed earlier attempts to demonstrate idiosyncratic skin reactions to drugs in albino rats. We had investigated the hypothesis that skin reactions to drugs could be due to marginal vitamin deficiencies, which may occur in man but are rarely

seen in albino rats fed a standard high vitamin laboratory chow.<sup>12</sup> Adult rats were fed a group of diets used by nutritionists to demonstrate vitamin deficiencies in weanlings and were given benzylpenicillin in relatively large doses. A fulminating lethal reaction followed in rats fed certain of those diets. This lethal reaction could not be prevented by vitamin supplementation, and it appeared to be due to large amounts of certain foodstuffs in the diet. For example, in a diet deficient in pantothenic acid for rats, carbohydrate is provided as sucrose; it was found that rats fed this diet ate an amount of sucrose per day which would kill them if given at one time on an empty stomach.<sup>13</sup> Of the various foodstuffs investigated to date, starch is by far the least toxic.

The rat responds to oral administration of large amounts of starch as it does to large amounts of unabsorbable substances such as kaolin<sup>14</sup> and barium sulfate.<sup>15</sup> The excess matter is pelleted and excreted, and death occurs from bowel obstruction if the animal is unable to move these large calculi along the gastrointestinal tract. Bowel obstruction could be produced in over 50% of albino rats by adminis-

TABLE IV.—WATER CONTENT OF BODY ORGANS IN ALBINO RATS AFTER 14 DAYS OF DAILY ORAL ADMINISTRATION OF STARCH AND OF DISTILLED WATER (DW)†

Organ	Group	Daily dose of starch (1st subheading line, g. per kg.) or distilled water (2nd subheading line, ml. per kg.)			
		36	72 - 120	168 - 204	240 - 288
		60	120 - 200	280 - 340	400 - 480
Adrenal glands.....	Starch	+4.3	-4.7	-5.6	-2.7
Adrenal glands.....	D.W.	+0.9	-7.9	-5.5	+0.4
Brain.....	Starch	+1.7	-0.9	-1.9	-1.3
Brain.....	D.W.	+0.8	-0.8	-2.2†	-1.0
Heart.....	Starch	-1.2	-2.8	-1.8	-2.1
Heart.....	D.W.	-0.1	-2.5†	-3.2†	-2.9†
Kidneys.....	Starch	+1.5	-3.8	-3.6	+0.8*
Kidneys.....	D.W.	-0.4	-4.9††	-5.0††	-4.6†
Liver.....	Starch	+3.0	+0.2	+5.7*	+4.4*
Liver.....	D.W.	+4.5	-2.3	+0.9	-1.4
Lungs.....	Starch	-0.5	-0.5	-3.0	-2.7
Lungs.....	D.W.	+0.8	0.0	-2.4	-1.9
Muscle (ventral abdominal wall).....	Starch	-4.5*	-2.5	-0.8	+0.1*
Muscle (ventral abdominal wall).....	D.W.	+4.9	-5.2††	-4.8†	-4.2
Skin.....	Starch	-4.1	+0.1	+1.4*	+3.6
Skin.....	D.W.	-1.4	-2.2	-4.3†	+1.5
Spleen.....	Starch	+1.4	-0.4	-2.1	0.0
Spleen.....	D.W.	+0.9	+0.2	-2.2†	-0.9
Submaxillary salivary glands.....	Starch	+1.0	-3.0	-3.9	-2.6
Submaxillary salivary glands.....	D.W.	-4.7	-7.0††	-8.5††	-7.3††
Testicles.....	Starch	+0.3	-1.9	-1.3	-2.3
Testicles.....	D.W.	+0.8	-2.0††	-1.3	-1.2
Thymus gland.....	Starch	-2.7	-1.3	-2.2*	-3.2
Thymus gland.....	D.W.	+1.3	-2.0	-4.9†	-3.2
Residual carcass.....	Starch	+2.5	-0.8	+0.4*	0.0
Residual carcass.....	D.W.	+1.3	-2.3	-3.0	+0.1

†Water content was measured as g. per 100 g. dry weight. The results are expressed as mean per cent change from controls given only gastric tube insertions, specifically as  $(\bar{X}_d - \bar{X}_c) / \bar{X}_c \times 100$  where  $\bar{X}_d$  is the mean in rats given starch or distilled water and  $\bar{X}_c$  the mean in tube-insertion controls. In animals given starch, \* indicates that the mean per cent change was significantly different from that in rats given distilled water at  $P = 0.05$  to  $0.02$  and \*\* at  $P = 0.01$  or less. In rats given distilled water, † indicates that  $\bar{X}_d - \bar{X}_c$  was significant at  $P = 0.05$  to  $0.02$  and †† at  $P = 0.01$  or less.

tration during one day of sufficient kaolin or barium sulfate, but starch had to be given daily for some seven weeks before it produced gastrointestinal obstruction in a similar percentage of animals. This occurred following absorption of most of the water from the starch paste, leaving usually a single large calculus or gastrolith in the stomach and many large starch calculi in the small bowel. Allan and Woodruff<sup>5</sup> reported a starch gastrolith in a young woman who had eaten three to four pounds of starch daily for one year. Hypertrophy of the gastrointestinal tissues, particularly of the circular fibres of the muscularis externa, permitted most rats to evacuate starch calculi in the stool.

Other signs of toxicity were inhibition of growth, anorexia, oligodipsia, mild hypothermia, diuresis, alkaluria and a stress reaction. Mild toxic changes were occasionally noted microscopically in the liver and kidney, and these were associated with capillary-venous congestion of several body organs. These signs occurred in controls given equivalent volumes of distilled water and could have been due largely to the water, although convulsions, a characteristic of water intoxication,<sup>16</sup> did not occur.

Anemia, which has been reported frequently in women addicted to eating starch,<sup>4, 6</sup> did not occur in our rats. This was due probably to the rats eating some 75% of their normal daily amounts of laboratory chow, a diet which contains vitamins and minerals in considerable excess of the animals' minimal needs. The results suggest that anemia in starch-addicted women is due to deficient intake of iron-containing foods rather than to starch. Edwards *et al.*<sup>2</sup> found the diet of pregnant cornstarch-eaters deficient in calories, protein, calcium, iron and most vitamins.

The response of the rat to absolute and partial starvation has been studied in this laboratory and the results suggest that starvation was not responsible for loss of body weight in rats given starch.<sup>17, 18</sup> For example, starvation produces gastric ulcers which were not present in starch-treated rats. While part of the loss in body weight (actually inhibition of growth) was due to the water vehicle, loss was significantly greater in starch-treated rats and must be listed as a sign of subacute starch intoxication. The starch-treated animals were also more susceptible to pneumonia.

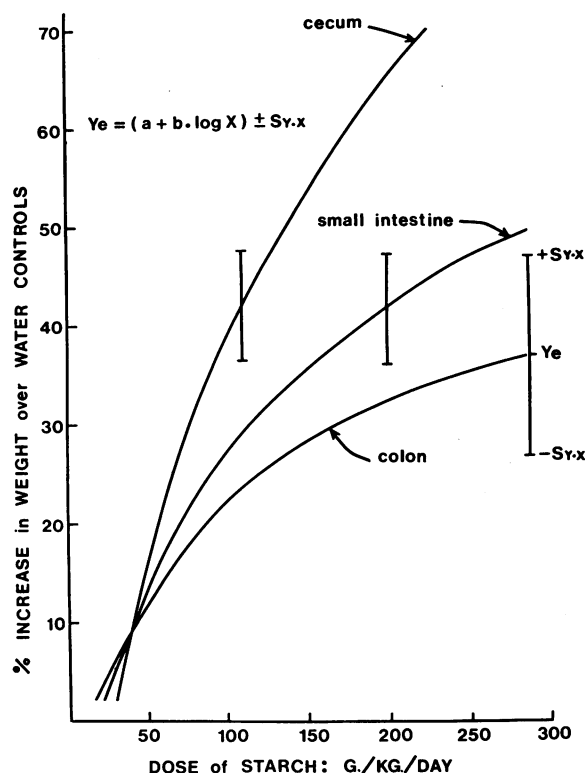


Fig. 3.—The regression, on daily dose of starch, of mean per cent increase in the weight of cecum, small bowel and colon over the respective weights in controls given distilled water. The values of "a" were -122, -69 and -44, of "b" 80.8, 48.3 and 32.8, and of  $S_{y \cdot x}$  or the standard error (S.E.) 5.7, 5.9 and 9.9 in the respective estimated value of Y in the equation  $Y = (a + b \log X) \pm S.E.$

Diets fed to albino rats seldom contain more than 75% starch.<sup>8</sup> Rats fed such a diet will eat from 40 to 100 g. of starch per kg. body weight per day, the younger animal eating relatively more.<sup>8</sup> When it is recalled that substances eaten with food over the 24 hours of the day are less toxic than when administered intragastrically at one time,<sup>19</sup> it would appear that a diet of 75% starch would produce no signs or minimal signs of toxicity due to the starch component.

**Summary** Addiction to starch eating has been reported mainly in Negro women of the United States of America. To investigate its toxicity, starch was given intragastrically as a paste in large doses to albino rats. Water was absorbed from the paste in the stomach and upper bowel, and the starch was converted to a calculus. Apparently in response to the extra work required to evacuate these calculi, there followed a considerable hypertrophy of the smooth muscle of the gastrointestinal tract. This permitted the administration of increasing daily doses of starch over a period of two to seven weeks. During this period doses of one-tenth body weight and above produced some inhibition of growth; doses of one-fifth body weight and above increased the susceptibility to pneumonia and bowel

obstruction owing to the inability of the animal to evacuate the starch calculi. It would not appear that doses of this order could readily be taken by man, and smaller doses had insignificant toxicity. Anemia reported in human starch addicts would appear to be caused by dietary deficiencies rather than by the starch intake.

**Résumé** L'habitude de manger de l'amidon a été surtout constatée chez les négresses des Etats-Unis d'Amérique. En vue d'étudier la toxicité de cet aliment, nous l'avons donné à fortes doses sous forme de pâte, par voie intragastrique à des rats albinos. L'eau étant absorbée à partir de la pâte dans l'intestin et la première portion de l'intestin, l'amidon s'est transformé en calcul. On a alors constaté une hypertrophie considérable du muscle lisse du tractus gastro-intestinal, cette réaction étant probablement la conséquence du travail supplémentaire exigée de l'organisme pour évacuer ces calculs. Cette hypertrophie a permis d'administrer des doses quotidiennes croissantes d'amidon sur une période variant de deux à sept semaines. Pendant cette période, des doses quotidiennes allant jusqu'au 1/10ème du poids corporel ou au delà de ces doses ont entraîné un certain retard de la croissance; des doses d'au moins 1/5ème du poids ont augmenté la prédisposition à la pneumonie et à l'occlusion intestinale, causée par l'impossibilité pour l'animal d'évacuer les calculs d'amidon. Il ne semble guère possible de faire prendre à l'homme des doses aussi considérables et, d'autre part, les doses faibles n'ont guère de toxicité. Quant à l'anémie signalée chez l'homme qui est accoutumé à absorber de l'amidon, elle est probablement l'effet d'une insuffisance alimentaire et ne paraît pas pouvoir être reliée à l'ingestion d'amidon.

#### REFERENCES

1. An urge for Argo: *Time* (Canada Edition), 90: 52, July 28, 1967.
2. EDWARDS, C. H. et al.: *J. Amer. Diet. Ass.*, 35: 810, 1959.
3. MERKATZ, I. R.: *New Eng. J. Med.*, 265: 1304, 1961.
4. SAGE, J. C.: The practice, incidence and effects of starch eating on Negro women at Temple University Medical Center, M.Sc. (Internal Medicine) Thesis, Temple University School of Medicine, Philadelphia, 1962.
5. ALLAN, J. D. AND WOODRUFF, J.: *New Eng. J. Med.*, 268: 776, 1963.
6. WARSHAUER, S. E.: *Southern Med. J.*, 59: 538, 1966.
7. CZERNY, A. D. AND KELLER, A.: *Des Kindes Ernährung, Ernährungsstörungen und Ernährungstherapie*, vol. 2, Franz Deuticke, Leipzig, 1909, p. 62.
8. DE CASTRO, E. S. AND BOYD, E. M.: *Proceedings of the Canadian Federation of Biological Societies*, 10: 108, 1967 (abstract).
9. LIU, S. J. AND BOYD, E. M.: *Ibid.*, 10: 49, 1967 (abstract).
10. WHISTLER, R. L. AND PASCHALL, E. F., editors: *Starch: chemistry and technology*, vol. 1, Academic Press Inc., New York, 1965.
11. CROXTON, F. E.: *Elementary statistics with applications in medicine and the biological sciences*, Dover Publications Inc., New York, 1959.
12. BOYD, E. M., MULROONEY, D. A. AND SARGEANT, E. J.: *Canad. J. Biochem. Physiol.*, 40: 1685, 1962.
13. BOYD, E. M. et al.: *Canad. J. Physiol. Pharmacol.*, 43: 47, 1965.
14. BOYD, E. M., COVERT, E. L. AND SHANAS, M. N.: *Industr. Med. Surg.*, 34: 874, 1965.
15. BOYD, E. M. AND ABEL, M.: *Canad. Med. Ass. J.*, 94: 849, 1966.
16. BOYD, E. M. AND GODI, I.: *Industr. Med. Surg.*, 36: 609, 1967.
17. PETERS, J. M.: *Growth*, 31: 191, 1967.
18. PETERS, J. M. AND BOYD, E. M.: *J. Nutr.*, 90: 354, 1966.
19. BOYD, E. M.: *Canad. Med. Ass. J.*, In press.